Attorney's Docket No.: 41260.003 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:

Stanley C. Antosh and Anthony J. Meduri

Serial No.: 10/710,710

Filed: 07/29/2004

For the Invention of:

USE OF METHYL PYRUVATE FOR THE PURPOSE OF INCREASING MUSCLE ENERGY PRODUCTION

Group Art Unit No. 1614

Examiner: Joseph S. Kudla

Telephone: (571) 270-3288

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

DECLARATION OF STANLEY C. ANTOSH

I, Stanley C. Antosh, hereby declare and state:

1. I am co-inventor of the invention in the above-referenced patent applications and I am authorized to make this declaration on behalf of the Applicants.

2. I have very carefully reviewed the Examiner's statements set forth in the Office Action of December 5, 2007 wherein the Examiner in effect has said that he doesn't believe that the invention will work. I respectfully disagree with the Examiner.

3. Attached to this Declaration are copies of experimental tests which clearly prove that the invention works. These include the following:

3.1 Attached hereto as **Exhibit 1** is a study entitled Methyl Pyruvate Ventura College Clinical Study by Ranya Alexander MD PhD, Tony Meduri PhD Dsc, James Perkins DC QME, Kevin Dunn DC QME.

3.2 Attached hereto as **Exhibit 2** is a study by Donald P. Orofino, M.D. setting forth the results of a test using methyl pyruvate to show that it increases energy production.

3.3 Attached hereto as **Exhibit 3** is the study entitled Methyl Pyruvate Diabetes Clinical Study by Donald P. Orofino MD, Tony Meduri PhD Dsc and Ranya Alexander MD, PhD.

3.4 Attached hereto as **Exhibit 4** is a true and correct copy of the study Methyl Pyruvate Parkinson's Observational Study by Ron Partain RPH, C.C.N., Ranya Alexander MD PhD, James Perkins DC QME, Tony Meduri PhD Dsc and Kevin Dunn DC QME.

I incorporate the exhibits in the argument set forth below.

Summary of Argument

By definition cellular fatigue is the absence of energy or ATP. The fatigue, exhaustion and ultimate death of a neuron, cardiac or muscle cell provides classic examples of cellular fatigue and the clinical consequences that result. Hence the effective transport, cellular and mitochondrial access and utilization of nutrients to support and sustain cellular energy (ATP) output leads to the health and restoration of organ functionality.

Muscle cells like all animal cells require energy to survive and perform their physiological functions. It is generally recognized that the main source of energy for cells is the glucose and oxygen delivered by the blood. Due to an explosion of interest in conditions of the nervous system, in recent years, neuroscientists have made considerable progress in understanding the mechanism by which energy deficiency leads to neuronal degeneration. It is incontrovertible that when brain tissue deprived of a fresh source of nutrients, from a stroke or insufficient nutrient-rich blood supply, will undergo first cellular fatigue then cell death.

There are two major components to the process by which all cells utilize glucose and oxygen to produce energy. The first component entails anaerobic conversion of glucose to pyruvate, which releases a small amount of energy, and the second entails oxidative conversion of pyruvate to carbon dioxide and water with the release of a large amount of energy (these metabolic processes have been detailed in biochemical texts).
Pyruvate is continuously manufactured in the living organism, including the CNS, from glucose. The process by which glucose is converted to pyruvate involves a series of enzymatic reactions that occur anaerobically (in the absence of oxygen). This process is called "glycolysis". A small amount of energy is generated in the glycolytic conversion of glucose to pyruvate, but a much larger amount of energy is generated in a subsequent more complicated series of reactions in which pyruvate is broken down to carbon dioxide and water. This process, which does require oxygen and is referred to as "oxidative respiration," involves the stepwise metabolic breakdown of pyruvate by various enzymes of the Krebs tricarboxylic acid cycle and conversion of the products into high energy ATP (adenosine tri phosphate) molecules by electron transport chain reactions.

Neurons as a classic example of cellular energy utilization. It is recognized that various defects in the cell's ability to utilize energy substrates (glucose and oxygen) to maintain its energy levels can also trigger an excitotoxic process leading to death of neurons. It has been postulated that this is the mechanism by which neuronal degeneration occurs in neurological diseases such as Alzheimer's dementia, Parkinsonism, Huntington's Chorea and amyotrophic lateral sclerosis. For example, evidence for defective intracellular energy metabolism has been found in samples of tissue removed by biopsy from the brains of patients with Alzheimer's disease and this has been proposed as the causative mechanism that triggers an unleashing of the excitotoxic potential of glutamate with death of neurons in Alzheimer's disease thereby being explained by an energy-linked excitotoxic process. Evidence for an intrinsic defect in intracellular energy metabolism has also been reported in Parkinsonism and Huntington's Chorea.

There is abundant evidence that ATP -sensitive K+ (KATP) channels link metabolic state to ATP, protein synthesis and dopamine cell excitability. The regulation of KATP channels in substantia nigra dopamine neurons by hydrogen peroxide (H2O2), which is produced in all cells during aerobic metabolism is omnipresent. Blockade of KATP channels or depletion of intracellular H2O2 increases the spontaneous firing rate of all dopamine neurons tested. Thus, endogenous H2O2 modulates neuronal activity via KATP channel opening, thereby enhancing the reciprocal relationship between metabolism and excitability.

Virtually all of the conditions which involve all cellular energy deficiency whether by substrate (nutrient) unavailability, DNA miscoding, receptor or other post translational protein alterations are recognized in clinical medicine as organ and tissue failure and in these comments on the CNS, as brain damage. Research into the effective resuscitation of brain is now focused on the "resuscitation" of individual brain cells.

In a (May 3) issue of Nature, quoting UCLA and Korean investigators as stating. "This [investigation] clearly suggests that mitochondrial failure is the central mechanism in the pathogenesis of Parkinson's disease." Also, a study published in the Proceedings of the National Academy of Sciences concluded: "The causes of Parkinson's disease are unknown. Evidence suggests that mitochondrial dysfunction and oxygen free radicals may be involved in its pathogenesis" and the in October 2002 Archives of Neurology Shults, et al note "evidence of slowing of the functional decline and mitochondrial therapy for Parkinson Disease."

Similarly, mounting evidence indicates that Alzheimer's disease (AD) is the result of cumulative failed or compromised mitochondrial processes. Experts have long known that a buildup of Beta-amyloid protein 'plaques' around and between neurons is a hallmark of AD. Recent studies at Cornell University (Dr. Gunnar Gouras, Weill Cornell Medical College) indicate that clumping of B-amyloid plaques between cells is not the problem, but rather they've found that the origins of AD are the result of events occurring *inside* the cell. B-amyloid hinders the cellular cleaning process, 'endocytosis' by blocking the unbiquitin-proteosome system –a system that has long been implicated in Parkinsonism and other degenerative brain diseases. Recent studies from OHSU (Dr. H. Reddy, Neurological Sciences Institute) indicate that the B-amyloid precursor protein accumulates within mitochondria leading to oxidative damage and increased levels of H2O2. This model predicts an ever-worsening, vicious cycle of damage to brain cells. Further Dr. Y. Huang at the Gladstone Institute of Neurological Disease in San Francisco has shown that another AD-linked protein called ApoE gets inappropriately processed resulting in a toxic fragment unable to be endocytosed, resulting in cytosolic accumulation. Indications are that these fragments interfere with glucose metabolism in mitochondria, again leading to mitochondrial dysfunction and neuronal death.

Although the above illustration focuses on the CNS, the need for "resuscitation" and reversal of cell fatigue (or, perhaps more appropriately, mitochondrial function fatigue),

in order to promote optimization of cellular genetic potential, is universally applicable in all animals cells.

A molecular product is herein introduced which aids in cellular access of a recognized metabolic substrate to ATP which promotes intracellular information transfer or signaling.

Methyl Pyruvate (MP)

The utilization of MP is more efficient that pyruvate in cellular systems already tested. MP was found to be more efficient than pyruvate in supporting intra-mitochondrial conversion of pyruvate metabolites to amino acids, Laboratory evidence is mounting to show that , by comparison with exogenous pyruvate, its methyl ester (MP) is preferentially metabolized in the mitochondria of tested cell preparations.

In accordance with the invention, a significant benefit of increased energy is accorded the human and animal that ingests or infuses the methyl ester of pyruvic acid.

Without claiming limitation of scientific theory, it is believed that esters of pyruvic acid provide the pyruvate molecule with significant lipophilic properties. The methyl ester, in particular, provides significant lipophilic "fat loving" attraction to gain entry into cells faster than equimolar amounts of free pyruvic acid or any tautomeric form of pyruvic acid.

As is well known to one skilled in the art, methyl pyruvate or pyruvic acid methyl ester may exist in one of several charged or tautomeric forms. The terms "pyruvic acid" and "pyruvate" are used interchangeably, all describing the various tautomeric and charge states of pyruvic acid.

Methyl refers to the straight chained alkyl group containing a single carbon with 3 attached hydrogen atoms and is wholly attached to the terminal oxygen of pyruvate in an "ester" formation. The term methyl pyruvate " refers to all tautomeric and charged forms of the compound.

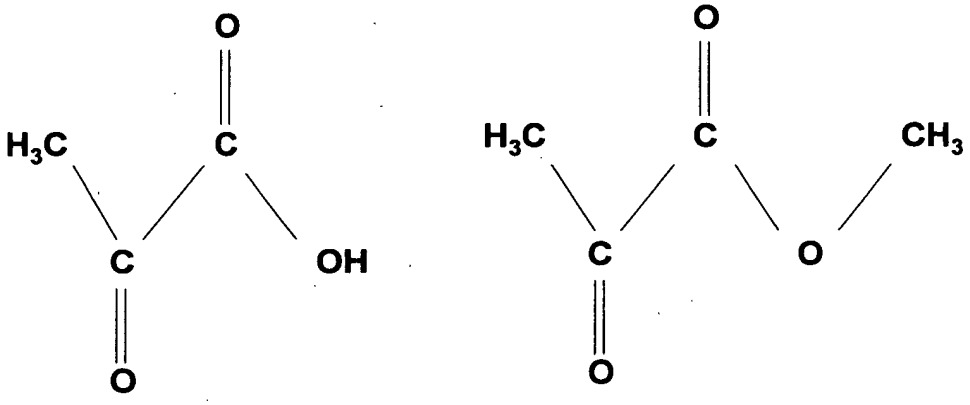
The following article referenced refers to the potential of membrane permeability (lipophilicity or "fat loving") and methylation using the CNS as an example of the focus of delivery and the blood brain barrier (BBB) as the membrane. Although the statement which follows focuses on the CNS, membrane permeability and the requirement of lipophilicity of a molecule for transport across the cell membrane and subsequent effect, is universally applicable.

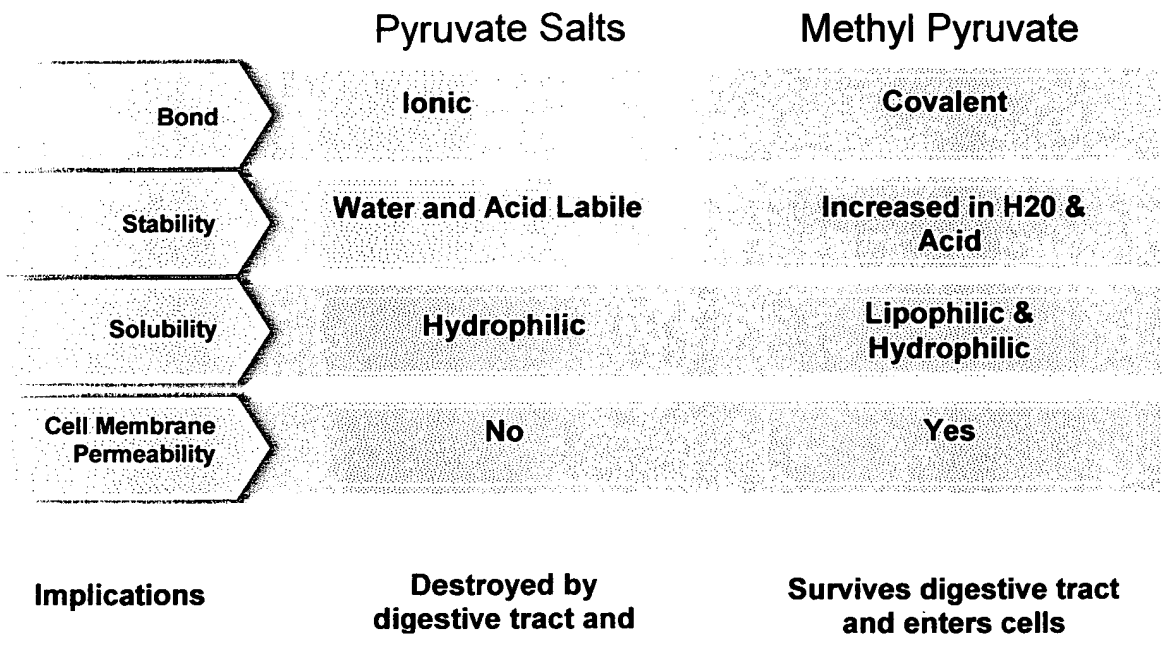
Although specific transport mechanisms are perhaps the best targets to focus CNS delivery strategies, the most simplistic route of enhancing the passive diffusion of peptides (i.e., increasing the lipophilicity) remains a viable method for increasing brain uptake. Lipophilicity has been shown to be a major determinant for the ability of a drug to diffuse across a membrane and remains one of the better tests for *in vivo* peptide

permeability, although this is highly dependent on the peptides studied. Lipophilicity can be increased by reduction of hydrogen bonding potential and/or addition of lipophilic groups. Reduction of hydrogen bonding potential has been shown to increase BBB transport for a number of substances, including small peptides. Methylation can reduce the overall hydrogen bonding potential of peptides and increases membrane diffusion by enhancing lipophilicity. [Antosh and Meduri unpublished article]

Banks WA, Kastin AJ. Peptides and the blood-brain barrier: lipophilicity as a predictor of permeability. *Brain Res Bull* 15: 287–292, 1985.].
Buchwald P, Bodor N. Octanol-water partition: searching for predictive models. *Curr Med Chem* 5: 353–380, 1998.
Buchwald P, Bodor N. Octanol-water partition of non-zwitterionic peptides: predictive power of a molecular size-based model. *Proteins* 30: 86–99, 1998.
Chikhale EG, Ng KY, Burton PS, Borchardt RT. Hydrogen bonding potential as a determinant of the in vitro and in situ blood-brain barrier permeability of peptides. *Pharm Res* 11: 412–419, 1994.

In the drawings that follow is the effective difference between pyruvate and methyl pyruvate. Without claiming limitation of scientific theory, it is believed that the methyl group (CH3) and the covalent bond stability are the structural difference (increasing the lipophilicity) that allows transport of the exogenous methyl pyruvate across the cell membrane and into the mitochondria thereby engaging enzymes of the Krebs tri-carboxylic acid cycle and conversion of the molecular constituents into high energy ATP molecules by electron transport chain reactions.





The present invention relates to the field of muscle stimulation and more particularly to enhancing the production of the energy by utilizing methyl pyruvate compounds, which modulate the system. This modulation will allow contractions and expansions in the muscles of mammals. Typical dosages of methyl pyruvate compounds will depend on factors such as size, age, health and fitness level along with the duration and type of physical activity.

Another aspect of the invention is its ability to enhance physical performance and activity by a human or animal after ingestion an effective amount of a composition of the invention embodied as methyl pyruvate.

Physical performance refers to objective and subjective belief that improved and greater physical ability stems from the ingestion of a composition containing the present invention.

Without wising to be bound by theory, it is believed that the provision of pyruvic acid resulting from ester hydrolysis or methyl pyruvate provided by a composition of the invention facilitates the increase in flux through the mitochondrial tricarboxylic acid cycle, thereby providing for the enhancement of (ATP) energy production in all cells of humans and animals.

Benefits of Methyl Pyruvate and increased ATP energy

Anecdotal and clinical reports of benefits below (included but are not limited to) listed are from more than 300 people in varying health between the ages of 18 – 92 who ingested a liquid composition of between a .5 gram – 5 gram dose of methyl pyruvate in various amounts of water (between 250cc and 1000 cc) or ingested methyl pyruvate in capsule, pills, tablets and as a granular.

Anecdotal and Clinical data - the Methyl Pyruvate benefits reported:

> Immediate reservoir of energy and stamina
> Enhanced recovery between sets in a workout and between workouts
> Heightened sense of awareness, association and mental clarity
> Improved mood and ability to concentrate
> Ability to work longer and with fewer breaks
> Staying power
> Much greater endurance
> Overall higher performance and intensity outputs
> Rapid "bounce back" from stress... mental-physical
> Diminished tremor
> Diminished insulin needs
> Diminished Parkinson's symptoms
> Diminished peripheral neuropathy
> Resolved IBS
> Improved renal function
> Improved hepatic function
> Improved immune function
> Improved cardiac function

Example 1- Strength and endurance

A group of 20 male college athletes were treated in double blind fashion with an oral ingestion of methyl pyruvate or placebo. The test group was given a one (1) gram dose of methyl pyruvate four times per day in 32 ounces of water each time. The placebo group was given equal amounts of water only. Both strength and speed were endurance with the treated group showing a significant increase in both strength and endurance after ingestion. (see below)

Ventura College Study Validates Efficacy of Methyl Pyruvate in Enhancing Physical Performance

Trial Design: Randomized Controlled Double Blind Placebo. 20 trained Male College Athletes, over 14 days.

Primary Endpoints: Study the Efficacy of Methyl Pyruvate in Measured Strength and Timed Endurance Tests.

Trial Results: Decrease of more than 7% in the 1.5 mile run time. Increase of more than 9% in strength (weight lift repetition). Methyl Pyruvate gains were ~10% vs. ~3% in placebo.

Conclusion from Study: Methyl Pyruvate engenders both aerobic and an-aerobic benefits in highly trained young adult males.

Without being bound by scientific theory the inventors believe that the structure of methyl pyruvate (and structure of pyruvate for lack of effect in the following referenced article), accounts for the properties unique to methyl pyruvate thereby engendering an increase in ATP energy synthesis resulting in the above described increases in aerobic and an-aerobic athletic performance in highly trained individuals.

Morrison, et. al., determined that oral ingestion of salts (e.g. calcium pyruvate, sodium pyruvate, etc) of pyruvate had no effect on participants.

Morrison MA, Spriet LL, Dyck DJ. Pyruvate ingestion for 7 days does not improve aerobic performance in well-trained individuals. Department of Human Biology and Nutritional Sciences, University of Guelph, Ontario, Canada. J Appl Physiol. 2000 Aug;89(2):549-56.

Example 2 – Parkinson's disease and dopamine

A group of 15 individuals with Parkinson's disease or Parkinson's symptoms were enrolled in a study given a (1) gram dose of methyl pyruvate two times per day. The objective of this observational trial was to quantify the effects (if any) of ingested methyl pyruvate (a dietary supplement) on intracellular energy levels required above baseline maintenance to produce ATP driven dopamine and "noticeable energy" with improvement of symptoms in humans diagnosed to have Parkinson's Disease or Parkinson's symptoms.

Parkinson's disease occurs when a group of cells in an area of the brain called the substantia nigra begin to malfunction and die. These cells in the substantia nigra produce a chemical called dopamine. Dopamine is a neurotransmitter, or chemical messenger, that sends information to the parts of the brain that control movement and coordination. When a person has Parkinson's disease, their dopamine-producing cells begin to die and the amount of dopamine produced in the brain decreases. Messages from the brain telling the body how and when to move are therefore delivered more slowly, leaving a person incapable of initiating and controlling movements in a normal way.

Parkinson's disease can also cause several different symptoms. The specific group of symptoms that an individual experiences varies from person to person. Some of the most common symptoms of Parkinson's disease are:

- tremor of the hands, arms, legs, jaw and face
- rigidity or stiffness of the limbs and trunk
- bradykinesia or slowness of movement
- postural instability or impaired balance and coordination

Summary:

Methyl Pyruvate Parkinson's Case Study Validates Efficacy of Methyl Pyruvate in improving or eliminating symptoms of Parkinson's disease.

Trial Design: Observational study with 15 humans diagnosed with Parkinson's disease or suffering from Parkinson's symptoms over 180 days.

Primary Endpoints: Study the Efficacy of Methyl Pyruvate in improving symptoms of Parkinson's disease.

Trial Results: Reported/observed improvement or elimination of symptoms.

1. tremor of the hands, arms, legs, jaw and face
2. rigidity or stiffness of the face, limbs and trunk
3. slowness of movement, talking.
4. impaired balance and coordination

Conclusion from Study: Methyl Pyruvate engenders both an increase in "noticeable energy" promoting a feeling of well being and improvement or elimination of symptoms in humans with Parkinson's disease or Parkinson's symptom.

Example 3 - Glucose control

A group of 12 poorly controlled Type I and Type II diabetics were enrolled in a clinical study given a (1) gram dose of methyl pyruvate two times per day. The study was conducted to determine the efficacy of methyl pyruvate at lowering Glycosylated Hemoglobin (A1c), (see explanations pg.10-11) FBS (fasting blood sugar) and insulin resistance in diabetics. We ended the 3 month clinical with usable HbA1c data on 11 individuals. The HbA1c and FBS data on all of the 11 participants was a significant lowering of HbA1c by 1% and FBS between 20-50 points (ex. prior to the study FBS was 150-180). The most dramatic drop in FBS was in the more severe, longer term diabetics of between 50 – 100 points (ex. prior to the study FBS was 180 - 220). Most notably, a female Type I diabetic since 1960 had her FBS (drop from about 350 to about 250) and A1c plummet from 9.1 to 6.5 - she had to reduce her daily insulin injections by >20U.

Without being bound by scientific theory, it is believed that methyl pyruvate does induce the same increase in mitochondrial metabolism and ATP in these diabetics as was seen in the athletes mention above. This increase in ATP is the molecular instrument that enables cells to operate in a more efficient way (cellular homeostasis or equilibrium), thereby allowing for increased function and cellular repair. In this particular instant disease of

diabetes, the most plausible theory is increased mitochondrial metabolism and ATP production leads to increased cellular metabolism (clearance) of glucose and triglycerides allowing for more proper insulin-responsive GLUT4 function and lowering of insulin resistance, FBS and HbA1c.

This study is important because reports in the scientific literature over the last several years suggest that regulation of energy can improve insulin sensitivity.

There is growing evidence that insulin resistance results in part from energy deficiency, leading to oxidative stress, chronic inflammation and may be responsible for the inducement of insulin resistance leading to type 2 Diabetes.

Summary:

Methyl Pyruvate Diabetes Clinical Study Validates Efficacy of Methyl Pyruvate in decreasing HbA1c and insulin resistance of individuals with Type 1 or Type 2 Diabetes Mellitus.

Trial Design: Single center clinical study with 12 humans diagnosed with Type 1 or Type 2 Diabetes Mellitus.

Primary Endpoints: Study the efficacy of ingested methyl pyruvate in decreasing HbA1c and insulin resistance of individuals with Type 1 or Type 2 Diabetes Mellitus.

Trial Results: Confirmed in clinical setting a decrease of HbA1c and insulin resistance:

12 Patients: Type I & II Diabetes (HbA1c between 5.7 – 12.1)

Treatment with methyl pyruvate at 2 g, 2X/day for 3 months. No other changes.

Result: No relevant changes in: Total protein, Albumin, Globulin, A/G ratio, BUN, Calcium, Iron, Chloride, Calcium, Bilirubin, Alk Phos, AST, Phosphorus, G-GTP, Cholesterol, WBC, RBC, Creatinine, BP, or weight. No SAEs or AEs.

However:

Average starting HbA1c: 7.5
Average 1 month HbA1c: 7.0
Average 2 month HbA1c: 7.1
Average 3 month HbA1c: 6.5

Three months of methyl pyruvate has lead to a decreased risk of:

CV disease by >20%
Micro-vascular disease by >40%
Death by >25%

Conclusion from Study: Methyl Pyruvate lowers HbA1c, insulin resistance and blood glucose in individuals with Type 1 or Type 2 Diabetes Mellitus and engenders an increase in "noticeable energy" promoting a feeling of well being with improvement of related symptoms of Diabetes Mellitus.

Explanation of Terms:

Homeostasis : The tendency of an organism or cell to regulate its internal conditions, such as the chemical composition of its body fluids, so as to maintain health and functioning, regardless of outside conditions. The organism or cell maintains homeostasis or equilibrium by monitoring its internal conditions and responding appropriately when these conditions deviate from their optimal state. *The American Heritage® Science Dictionary*

Protein synthesis: Protein synthesis is a process when cells build proteins which are widely used in cells to serve diverse functions. For example insulin is a hormone and like many hormones insulin is a protein with effects for transport and cell signaling. Dopamine, (a member of the catecholamine neurotransmitter family and a precursor to nor-adrenaline and then adrenaline, dopamine is synthesized in the body mainly by nervous system from the amino acid L –tyrosine) and acts to catalyze certain reactions. Other proteins include structural and enzymatic proteins which initiate cellular repair and function. It is well known that all of the above proteins require ATP energy for synthesis.

Diabetes or diabetes mellitus , chronic disorder of glucose (sugar) metabolism caused by inadequate production or use of insulin, a hormone produced in specialized cells (beta cells in the islets of Langerhans) in the pancreas that allows the body to use and store glucose. It is a leading cause of death in the United States and is especially prevalent among African Americans. COLUMBIA ENCYCLOPEDIA

Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response within cells. Insulin resistance in fat, muscle and liver cells reduces the effects of insulin and results in high plasma levels of insulin and glucose leading to Type 2 Diabetes including its complications.

FBS, Fasting blood glucose: A method for learning how much glucose (sugar) there is in a blood sample taken after an overnight fast. The fasting blood glucose test is commonly used in the detection of diabetes. A blood sample is taken in a lab, doctor's office, or hospital. The test is done in the morning before the person has eaten. The normal, non-diabetic range for blood glucose is from 70 to 110 mg/dl, depending on the type of blood being tested. If the level is over 140 mg/dl, it usually means the person has diabetes (except for newborns and some pregnant women). MedlinePlus Medical Encyclopedia: Glucose test

Glycosylated Hemoglobin A1c, (HA1c HbA1c): HbA1c is a test that measures the amount of glycosylated hemoglobin in your blood. Glycosylated hemoglobin is a molecule in red blood cells that attaches to glucose (blood sugar). You have more glycosylated hemoglobin if you have more glucose in your blood. The test is becoming the best measure of diabetic disease management and predictor of overall cardiovascular disease. Studies in the US and abroad have found that improved glycemic control benefits people with diabetes. In general, every percentage point drop in A1C blood test results (e.g., from 8.0% to 7.0%) reduces the risk of microvascular complications (eye, kidney, and nerve diseases) by 40% (American Diabetes Association).

GLUT4: As is well known to those skilled in the art, the GLUT4 isoform is the major insulin-responsive transporter that is predominantly restricted to striated skeletal and cardiac muscle and adipose tissue. In contrast to the other GLUT isoforms, which are primarily localized to the cell surface membrane, GLUT4 transporter proteins are sequestered into specialized storage vesicles that remain within the cell's interior under basal conditions. As post-prandial glucose levels rise, the subsequent increase in circulating insulin activates intracellular signaling cascades that ultimately result in the translocation of the GLUT4 storage compartments to the plasma membrane. Importantly, this process is readily reversible such that when circulating insulin levels decline, GLUT4 transporters are removed from the plasma membrane by endocytosis and are recycled back to their intracellular storage compartments. Numerous studies have demonstrated the importance of normal GLUT4 expression and cellular localization in regulating glucose homeostasis. It is estimated that up to 70% of blood glucose is cleared by GLUT4 in muscle.

Bonadonna RC, Saccomani MP, Seely L, Zych KS, Ferrannini E, Cobelli C, DeFronzo RA: Glucose transport in human skeletal muscle: the in vivo response to insulin. *Diabetes*42 :191 –198,1993

Charron MJ, Brosius FC 3rd, Alper SL, Lodish HF: A glucose transport protein expressed predominately in insulin-responsive tissues. *Proc Natl Acad Sci U S A*86 :2535 –2539,1989

Charron MJ, Katz EB, Olson AL: GLUT4 gene regulation and manipulation. *J Biol Chem*274 :3253 –3256,1999

Wallberg-Henriksson H, Zierath JR: GLUT4: a key player regulating glucose homeostasis? Insights from transgenic and knockout mice (Review). *Mol Membr Biol*18 :205 –211,2001

I, Stanley C. Antosh, being hereby warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any resulting registration, declare that the facts set forth in this Declaration are true, all statements made of my own knowledge are true, and all statements made on information and belief are believed to be true.

Dated: 6-2-08

Stanley C. Antosh

Stanley C. Antosh

Methyl Pyruvate Ventura College Clinical Study

Ranya Alexander MD PhD, Tony Meduri PhD DSc,
James Perkins DC QME, Kevin Dunn DC QME

METHYL PYRUVATE STUDY

Subjects: college athletes

Title: The effect of ingested methyl pyruvate on specific aerobic and anaerobic performance of college athletics

Clinical Study Phase 1

Study duration: 14 days

Single center study:

The objective of the study is to determine whether methyl pyruvate ingestion (from 2/19/05 – 3/4/05) has a measurable effect on the performance of trained college athletics in accomplishing an-aerobic strength and aerobic endurance testing.

Number of subjects: 20

The tested product is methyl pyruvate liquid, 1cc (1gram) dose ingested orally 4 times per day for 14 days.

Reference therapy consists of a placebo liquid (containing natural fruit juices formulated to mimic methyl pyruvate taste and smell) of identical volume not containing methyl pyruvate

Statistical method: Standard t-test with paired measurements. Because of the low sample size (twenty total) paired measurements, one at baseline and one at the conclusion of the study must be used. The size of effect (difference between effect and non) considered statistically valid is to be determined.

1. This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedure.

1.1 **Background** Methyl pyruvate is a lipophillic derivative of pyruvate a natural product produced in the body. Methylation of pyruvate rendered is more available to cells and allows greater participation of an initiate of the tricarboxylic acid cycle (Krebs Cycle).

Anecdotal reports have shown that methyl pyruvate when taken orally, subjectively confers energy and stamina to the consumer presumably based on the increased adenosine triphosphate production and enhanced efficiency of cellular oxidative phosphorylation. Pyruvate in effect "primes" the TCA pump. This process would, presumably, render mitochondria more productive in a shorter period of time and increase athletic strength and endurance via a non-artificial nutritional mechanism, which does not involve adrenal stress or steroid or growth factor supplementation or augmentation.

1.2 **Investigational Agent:** Methyl Pyruvate – The energy requirements of most cells supplied with glucose are fulfilled by glycolytic and oxidative metabolism, yielding ATP. A membrane-permeant analog, methyl pyruvate, in pancreatic beta cells, produced a block of KATP, a sustained rise in [Ca2+], and an increase in ATP driven insulin secretion 6-fold the magnitude of that induced by glucose.

1.3 **Pre-Clinical data - Reports from 25 people between the ages of 29 - 76**
The MP benefits reported:
> Immediate reservoir of energy and stamina
> Enhanced recovery between sets in a workout and between workouts
> Heightened sense of awareness, association and mental clarity
> Improved mood and ability to concentrate
> Ability to work longer and with fewer breaks
> Staying power
> Much greater endurance
> Overall higher performance and intensity outputs
> Rapid "bounce back" from stress... mental-physical

1.4 **Dose rational and risk and benefits.** Original dose (range of 2-6 grams per day) assessment was based on results of in-vitro insulin secretion studies. Quantitative comparisons of glucose, glutamine, glutamic acid, luceine, pyruvate and methyl pyruvate on pancreatic beta-cells established a base-line reference. This theory was subsequently validated by anecdotal reports. Possible negative side-effects may include, but are not limited to gastro esophageal reflux, esophageal irritation, Transient visual disturbance.

2. **Study Objectives:** The objective of the study is to determine whether daily methyl pyruvate ingestion has a measurable effect on the performance of trained college athletes in accomplishing anaerobic and aerobic strength and endurance testing.

3. **Study design:** Randomized controlled double blind clinical trial

3.1 Primary endpoints- to study the efficacy of methyl pyruvate in increasing measured strength and timed endurance tests in college athletes.

3.2 Secondary endpoint- to underscore the taste and GI tolerability of the test dosage of liquid methyl pyruvate.

4. Subject selectivity

4.1 Inclusion criteria: Male college athlete, age 18-25 weight between 150-250 lbs

4.2 Exclusion criteria: Orthopedic injuries, cardiac, respiratory, metabolic disease or infections, use of any stimulant form (i.e. caffeine, nicotine. Ephedrine)

5. Methyl Pyruvate

5.1 Description: clear liquid with slight lactate odor and taste.

5.2 Dose and route of administration: 1cc (1gram) dose taken orally 4 times per day in 32 oz. water for 14 days.

5.3 Packaging for dosing: 20 identical commercial 1liter (PET) water bottles. 15 bottles will contain a mixture of 1 part methyl pyruvate and 30 parts water
5 bottles will contain the placebo mixture of natural fruit juices formulated to mimic the taste and smell of the methyl pyruvate – water mixture being tested
The test subjects will be instructed to further dilute their assigned liquid concentrate as follows: add 1 oz. (30cc) to 32oz. (1 quart) of water and drink morning, noon, mid afternoon, and late afternoon. The final ratio consumed is 1 part methyl pyruvate to 960 parts water.

6. **Blinding of study:** Twenty identical containers (size) will be labeled "A" through "T" and picked randomly to be filled with MP or placebo. A code sheet will be prepared by a non-investigator and contents of the labeled container will be logged and kept confidential.

7. **Participant's procedure:**

4 teams of 5 participants, each with a captain.

Day 1 - 7:00 AM (No stimulants of any kind on day of testing.)

Investigator Measures Baseline: blood pressure, heart rate, blood oxygen.
Each Player performs:

1. 1.5 mile timed run.

15-minute rest to clear lactic acid.

2. Maximum bench press repetitions with 135lbs

15-minute rest to clear lactic acid.

Investigator Measures: blood pressure, heart rate.

14-day supply of MP or placebo will be distributed to each participant to be orally ingested 1cc (1 gram) 4 times a day in 32 oz. water for 14 days.

Participants will conduct normal nutritional and exercise routines during testing intervals

Day 14 - 7:00 AM. MP taken 30 minutes prior to testing (No stimulants of any kind on day of testing.)

Each Player performs:

1. 1.5 mile timed run.

15-minute rest to clear lactic acid.

2. Maximum bench press repetitions with 135lbs

15-minute rest to clear lactic acid.

Investigator Measures: blood pressure, heart rate.

8. Safety and adverse effects: should subject become ill or infirmed, independent (code holder) non-investigator will determine if subject has had the Methyl Pyruvate and inform the subject and his coach

8.1 Stopping rules: Should more than one subject become ill and it proved that both (all) were test subjects and not controls, the clinical trials will end and the medical investigator report findings to all individuals and the coach. All adverse events must be recorded.

Summary:

Ventura College Study Validates Efficacy of Methyl Pyruvate in Enhancing Physical Performance

Trial Design: Randomized Controlled Double Blind Placebo. 20 trained Male College Athletes, over 14 days.

Primary Endpoints: Study the Efficacy of Methyl Pyruvate in Measured Strength and Timed Endurance Tests.

Trial Results: Decrease of more than 7% in the 1.5 mile run (endurance aerobic) time. Increase of more than 9% in strength (weight lift repetition an-aerobic). Methyl Pyruvate gains were ~10% vs. ~3% in placebo.

Conclusion from Study: Methyl Pyruvate engenders both aerobic and an-aerobic benefits in highly trained young adult males.

Double Blind Placebo Study 20 College Football Athletes

Subject		Age	Height	Weight	Group	Bottle	Run time	Run time	Diferenti	Lift reps	Lift reps	Differen	% change run	% change lift
Kristopfer Vasquez		20.00	6'0"	310.00	1.00	A	16.38	15.91	0.47	57.00	60.00	3.00	0.030	0.053
Johnny Dudley		19.00	6'2"	210.00	1.00	D	12.20	11.43	0.77	22.00	23.00	1.00	0.067	0.045
Luis Guzman		23.00	5'8"	160.00	1.00	E	13.66	12.80	0.86	26.00	29.00	3.00	0.067	0.115
Tristan Blakely		22.00	6'3"	215.00	2.00	J	10.90	10.26	0.64	20.00	25.00	5.00	0.062	0.250
Andrew Henggeler		19.00	6'4"	235.00	3.00	K	15.05	13.33	1.72	28.00	32.00	4.00	0.129	0.143
James Groen		19.00	6'1"	180.00	3.00	L	11.61	11.03	0.58	18.00	20.00	2.00	0.053	0.111
Rafael Horton	Track meet**	23.00	6'2"	247.00	1.00	C	14.83	14.29	0.54	45.00	40.00	-5.00	0.038	-0.111
David Herrera	Track meet**	21.00	6'0"	180.00	4.00	Q	9.28	8.75	0.53	26.00	23.00	-3.00	0.061	-0.115
Brandon Manoff		20.00	5'8"	205.00	3.00	N	12.66	11.66	1.00	45.00	48.00	3.00	0.086	0.067
Deaven Washington	Rt quad injury	18.00	6'1"	192.00	4.00	S	10.45	11.03	0*	16.00	22.00	6.00		0.375
Jimmie Griffin Jr.	Rt. Knee injury	19.00	6'2"	260.00	4.00	T	12.58	13.91	0*	33.00	35.00	2.00		0.061
Kyle Vanvales	Rt knee injury	19.00	6'3"	230.00	1.00	B	10.43	10.43	0*	27.00	28.00	1.00		0.037
Blake Smith	Rt. Ankle injury	19.00	6'2"	325.00	3.00	O	15.76	16.80	0*	33.00	38.00	5.00		0.152
Average							12.75	12.43	0.790	30.46	32.54	2.077	0.066	0.091
JD Probasco		19.00	6'5"	320.00	2.00	F	15.90	15.46	0.44	39.00	40.00	1.00	0.028	0.026
Curtis Bickly		19.00	5'11"	185.00	4.00	P	9.28	8.96	0.32	22.00	24.00	2.00	0.036	0.091
Robert Oschtska	Track meet**	22.00	6'4"	330.00	2.00	H	15.60	16.00	-0.40	35.00	35.00	0.00	-0.025	0.000
Steven Shell	Track meet**	21.00	5'11"	200.00	4.00	R	12.12	11.42	0.70	33.00	30.00	-3.00	0.061	-0.091
Tom Bueno		19.00	5'11"	185.00	3.00	M	11.23	11.20	0.03	27.00	30.00	3.00	0.003	0.111
Average							12.83	12.61	0.218	31.20	31.80	0.600	0.021	0.027
Tony Borrello	Droped Out	19.00	6'1"	280.00	2.00	I	16.06			40.00				
Djadji Daffe	Droped Out	21.00	6'5"	310.00	2.00	G	13.66			26.00				

Difference	Study Group	Placebo group	Differential	Gain with Encell over Placebo
Run	0.066	0.021	0.045	3X
Lift	0.091	0.027	0.064	3X

* Foot note athletes had leg injuries at time of 2nd run date were not included in stats for run
** foot note these 4 athletes participated in a track meet the day before testing was done

Anonymous comments from participant athletes, randomly assembled

1 My body seemed to recover faster and my workouts went faster — Caught a cold the night of the first test but stayed well enough to participate
2 Felt more energy
3 More energy and endurance
4 More energetic after a good work out
5 Felt a little more energy in the morning
6 No effect needs to improve taste
7 No effect
8 Had more energy throughout the day — EnCell work well but I don't feel I'm consistent enough for further study
9 focus was better easier to think, good sexual performance while I'm on the stuff — make it taste better
10 Dry cotton mouth increased libido
11 More energy and endurance
12 No effect
13 No effect
14 No effect
15 No effect
16 No effect
17 Felt energy but felt dizzy at times

VC Study

Subject	Age	Height	Weight	Group	Bottle	Run time 1	Run time 2	Differential	Lift reps 1	Lift reps 2	Differential
Curtis Bickly	19	5'11"	185	4	P	9.17	[illegible]		22		
David Herrera	21	6'0"	180	4	Q	9.17	8.45		26	23	
Kyle Vanvales	19	6'3"	230	1	B	10.26	[illegible]		27		
Deaven Washington	18	6'1"	192	4	S	10.27	11.02		16		
Tristan Blakely	22	6'3"	215	2	J	10.54	[illegible]		20		
Tom Bueno	19	5'11"	185	3	M	11.14	[illegible]		27		
James Groen	19	6'1"	180	3	L	11.37	[illegible]		18		
Steven Shell	21	5'11"	200	4	R	12.07	11.35		33	30	
Johnny Dudley	19	6'2"	210	1	D	12.12	[illegible]		22		
Jimmie Griffin Jr.	19	6'2"	260	4	T	12.35	[illegible]		33		
Brandon Manoff	20	5'8"	205	3	N	12.4			45		
Luis Guzman	23	5'8"	160	1	E	13.4	[illegible]		26		
Djadji Daffe	21	6'5"	310	2	G	13.4			26		
Rafael horton	23	6'2"	247	1	C	14.5	14.79		45	40	
Andrew Henggeler	19	6'4"	235	3	K	15.03	[illegible]		28		
Robert Oschtska	22	6'4"	330	2	H	15.4	16.0		35	35	
Blake Smith	19	6'2"	325	3	O	15.46	[illegible]		33		
JD Probasco	19	6'5"	320	2	F	15.54			39	40	
Tony Borrello	19	6'1"	280	2	I	16.04			40		
Kristopfer Vasquez	20	6'0"	310	1	A	16.23			57	60	
Brandon Chewning	21	5'10	160	no show							

VC Study

Subject	Age	Height	Weight	Group	Bottle	Run time 1	Run time 2	Differential	Lift reps 1	Lift reps 2	Differential
Curtis Bickly	19	5'11"	185	4	P	9.17	8.55		22	24	
David Herrera	21	6'0"	180	4	Q	9.17			26		
Kyle Vanvales	19	6'3"	230	1	B	10.26	10.26		27	28	
Deaven Washington	18	6'1"	192	4	S	10.27	11.02		16	22	
Tristan Blakely	22	6'3"	215	2	J	10.54	10.17		20	23	
Tom Bueno	19	5'11"	185	3	M	11.14	11.17		27	30	
James Groen	19	6'1"	180	3	L	11.37	11.07		18	20	
Steven Shell	21	5'11"	200	4	R	12.07			33		
Johnny Dudley	19	6'2"	210	1	D	12.12	11.76		22	23	
Jimmie Griffin Jr.	19	6'2"	260	4	T	12.35	13.47		33	35	
Brandon Manoff	20	5'8"	205	3	N	12.4	11.40		45	48	
Luis Guzman	23	5'8"	160	1	E	13.4	12.48		26	29	
Djadji Daffe	21	6'5"	310	2	G	13.4			26		
Rafael horton	23	6'2"	247	1	C	14.5			45		
Andrew Henggeler	19	6'4"	235	3	K	15.03	13.20		28	32	
Robert Oschtska	22	6'4"	330	2	H	15.4			35		
Blake Smith	19	6'2"	325	3	O	15.46	16.18		33	38	
JD Probasco	19	6'5"	320	2	F	15.54			39	40	
Tony Borrello	19	6'1"	280	2	I	16.04			40		
Kristopfer Vasquez	20	6'0"	310	1	A	16.23			57	60	
Brandon Chewning	21	5'10	160	no show							

Knee Injury

Hand strain

Ankle

1 case - $72.00

18 - Muscle Machine Choc.

DONALD P. OROFINO, M.D.
100 Manetto Hill Road - Suite 309
Plainview, New York 11803
TEL# (516) 433-3232 Fax# (516) 433-7802

May 13, 2008

Dear Stan,

The EnCell you have provided for my patients as a natural supplement has achieved outstanding results in 68 patients over the past 2 years.

Changes evaluated;

- Energy improvement
- Diminished tremor
- Diminished insulin needs
- Diminished Parkinsons symptoms
- Diminished peripheral neuropathy
- Resolved IBS
- Improved renal function
- Improved cardiac function
- Improved mental focus

The changes are so diverse that the mechanism of action must engender increased energy in the respective organs that demonstrate improvement.

I have demands that exceed your provision of EnCell. Please let my patients or myself know how we may have continued supplies. The need is urgent as symptoms are recurring slowly but surely without continued treatment.

Sincerely,

DONALD P. OROFINO, M.D.

JAMES P. PERKINS, D.C. QME

Sobol Orthopedic Medical Group
960 E. Green Street
Suite 206
Pasadena, CA 91106
Ph: (626) 449 - 8469
Fax: (626) 449 – 7910

Healing Access
9388 Telephone Rd.
Ventura, CA 93004
Ph: (805) 647-5657
Fax: (805) 647- 4583
Cell: (805) 264 – 9944

Mr. Stan Antosh
PO Box 2312
Palm Springs, CA 92263

December 12, 2004

Mr. Antosh,

I just wanted to quickly write and give you some feed back on the Methyl Pyruvate. I have used it as recommended 30 minutes prior to my work out. Most days, but not all, I experienced significant added power and endurance during my lift days and endurance during my cardio days. It really is quite surprising that there is no caffeine component here. I love the added endurance without the buzz (in my case, anxiety) and let down of caffeine laden sport drinks.

I did get dehydrated at first and have increased my water through out the day and that has abated.

I also noted clearness of thought, general warming sensation and increased libido. Has anyone else commented on that?

I recently caught a cold and ended up using your MP throughout the day. Wow, what a difference. It managed my symptoms: headache, achiness, runny nose etc during the day and only had the cold for about 3 days. I think you have a potential **cold formula** in there somewhere.

Overall I think you have something great in the development of performance enhancing drinks, far superior to anything out there that I've tried and I've tried most of them. Adrenal stimulation is what all of the others rely on, this does not, and your explanation of the mechanism is sound.

If I can help you get a study started please don't hesitate to call.

Sincerely,

Dr James P. Perkins DC QME

From: john Fitztgerald [mailto:wakecap@yahoo.com]
Sent: Thursday, May 08, 2008 12:07 PM
To: Stan Antosh
Subject: Encell and Me - Its a GREAT THING!!!!!!!!!!

I just wanted to take this opportunity to thank you for Encell. I am a 40 yr male working full hectic days in NYC. I truly burn the candle at both ends as the saying goes. I took Encell for the month of February and noticed a huge increase in my energy levels and mental alertness. I actually did not find the need for my afternoon coffee break needing to be perked up while on Encell. I had enough energy after the work day was over to actually hit the gym five times a week and then do paperwork all night. That is huge for me. I am always skeptical on everything so I went without Encell for the month of March and I noticed by the middle the first week I was back to my old routine, huge afternoon cups of coffee, dragging myself to the gym two times a week with no energy to workout and a hard time to concentrate late at night. I went back on Encell in April and found my energy levels increased just as it did in February. Thank you for helping me with the demands my body needs to survive, compete and to be healthy.

John Fitzgerald

November 15, 2004

Dear Mr. Edwin Levy:

While certainly it was my pleasure in speaking with you last, I now feel compelled to provide you with specific instances of my demise and previous condition and where I am now. My omission of these details was an attempt to maintain my dignity. This is a time when the pen is more powerful then the spoken word. I would be remiss to not do so, since I consider the disparity a miracle.

Three years ago I had the pleasure of meeting and befriending Stanley Antosh. At that time, I informed him that I was in my 5th year since having been diagnosed with Parkinson's and was taking four prescription drugs for PD. My statement to him was it appears that the medication is working and keeping PD at bay.

In my successive meetings (a few months) with Stanley, it was apparent that my health was rapidly declining into advanced critical, late stage PD. After months of living with this decline, I informed him that I had recently seen a neurologist MD from Loma Linda Medical University, who had told me in October of 2002 that I had 2 months to a wheel chair and 6 months to complete disability and placement in a nursing home or death. The doctor told me that this is the nature of the disease, and that his only recourse was to double the dosage of the 4 prescription medications, to no avail.

My next meeting with my friend Stanley was the day after the meeting with my Neurologist. I informed Stanley what the doctor had told me and he asked me "What did I want to do"? My response was, "that I wanted to stop taking the 3 medications, and only continue on Sinemet". I also asked him to develop a protocol of necessary nutrients, which will enable my body to repair itself or at least take the place of the drugs I had discontinued. He developed the protocol with his colleagues, and I have been complying with his nutrient list ever since. Stanley told me that ultimately, the goal was cessation of the progression of PD, and then regression. This is where I am today. The progression has stopped, and regression started.

Starting in July of 2004, I was consuming 1 gram of Methyl Pyruvate in 16 ounces of water 4 times per day. The effects were immediate and dramatic. At this time I was taking Sinemet, 250mg six times per day. I had been on this daily dosage level for two years, yet I still had tremors. With ingestion of the Methyl Pyruvate, the tremors subsided almost immediately. I noticed they reappeared 2 hours after my last Sinemet dosage, which was 2 hours before my next dosage, which was when I would consume the Methyl Pyruvate. One of the most noticeable benefits was my depression went away and I had both mental and physical energy. These benefits I attribute directly to Methyl Pyruvate as I

had been battling with depression and had no energy for 5 years. Imagine, the first time in 5 years I was neither depressed, nor lacking energy.

After two months on this protocol, with me reporting these benefits to Stanley, he asked me if I would be willing to try and reduce my Sinemet levels slowly. Of course I would, and my reduction of Sinemet commenced. From the first week of September until the 3rd week of October I was able to reduce my Sinemet from 250mg six times per day down to 250mg once per day. I recently had an appointment with my Neurologist and informed him of my miraculous condition. His only statement was that now would be a good time to have the brain surgery and electrode implantation; I declined his offer. He did agree to the new 125mg Sinemet prescription with Comtan. Where I am today, as a result of my reduction of Sinemet from 1500mg per day to 250mg per day, is indeed a miracle.

My side effects from 2 years of Sinemet at 1500mg per day were horrible balance, mental confusion, depression, drooling, dizziness, no energy (mental of physical). You must understand that when I informed you in our telephone conversation that I was on my hands and knees, I was literally on my hands and knees for weeks on end, because I couldn't walk, my legs wouldn't move. When I could walk I was bent over 90 degrees at the waist. I couldn't leave my apartment. I couldn't drive. I couldn't bathe. So I was literally crawling around my apartment on my hands and knees, but that's the good part! That's when I could move. There were days where I couldn't talk, or even move, I couldn't get out of my chair, I couldn't eat, I couldn't cook. I was in a diaper and couldn't even respond to my own body's needs. These symptoms, this condition I was in, is the dreadful fate that awaits those with PD.

Now, here is the greatest miracle of all. This molecule that Stanley has given me has not only changed my life by allowing me to reduce the Sinemet, but has changed other people's lives as well. To explain, all of the above-mentioned side effects and non-functioning conditions of my body and mind are gone and it is I who gives aid to all the other non-functioning senior citizens in my apartment complex. I drive them to the hospital; I drive them to the store. If they can't get out, I go grocery shopping for them or I just run down the block to get them a sandwich.

I used to pray for death, to look forward to dying. Now, I look to life and I am helping others to get theirs.

Yours truly

Robert Joyce

TESTIMONIAL CASE 001

Encellon Products:
Encell (Methyl Pyruvate)
Joint Pain Solution "Spray"

Observer: Stan Antosh

Observation dates: approx 6 months (4/1/07 thru 10/2/07)
Facility:
Nursing home - Palm Springs, CA

Subject: BILL

Male ex-truck driver
Ht (at peak health) approx 6'3",
Wt (at peak health) approx 205 lbs
Relatively inactive bedridden/ wheelchair since 8/2006;
Diet unlimited with emphasis on fruits and carbohydrates in facility

Pertinent Medical hx :
Type II DM gliberide, glucophage – started insulin 10 months prior.
HIV + since approx 1980; viral load- undetectable, T-cells >700
Lower extremity weakness, probable neuro-muscular degenerative MS vs ALS vs other (Dx ALS 4/2006), worsening open wounds on both feet since 2/2007
Gall Bladder removal 7/2006

CLINICAL COURSE

Initial presentation April 1 2007: In bed with bandages from toes to ankles. Skin shows dusky gray pallor from mid thigh to mid lower leg. Deep maroon to purple (ecchymosis) from 9" above ankle to toes. Toes most deeply discolored. Bilateral lower extremity edema (swelling) throughout. Complete numbness since 10/2006.

Day 1: Pt began taking Encell 2 grams per day in water (1 gram each AM and PM). Prior AM fasting blood sugars on Insulin previous 10 months (FBS) approx 250- 300 mg/dl

Pt began with spray three times per day entire length of visible leg and feet from mid thigh to toes

Day 3: Observer notes "gray begins to resolve above knee to approx 6" below knee." FBS spikes to 360

Day 5: gray has subsided completely above ankle, decreasing maroon color in toes

Day 8: FBS spike remains at between 360 - 400 since day 3.

Day 9: FBS 266, normal color returning throughout, rosy pink color returned to toes

Throughout 2nd week FBS 250- 260

3rd week FBS 230-240

End of 4th week FBS < 200 for the first time in years and the sensation has returned to legs, feet and toes with decreasing edema. Pt continues JPS spray 3xs/per day from mid-thigh to toes and raises Encell ingestion to 3 grams per day (AM, lunch and PM).

End of 9th week Pt is off insulin (for 1st time since 8/2006) after 5 weeks of FBS between 150 - 225

End of 13th week variation in FBS 72, 126, 90 with reported no leg edema.

End of 19th week variation of FBS for previous 5 weeks 43 – 96.

20th – 27th week, FBS, <100mg/dl, both leg wounds completely healed by week 23.

Current: Off insulin; Pt continues JPS spray 3xs/per day from mid-thigh to toes and Encell ingestion of 3 grams per day (AM, lunch and PM) continues gliberide,(?) glucophage.

From: Christine Lyszczasz [mailto:common.sense.medicine@gmail.com]
Sent: Thursday, April 24, 2008 9:09 AM
To: santosh@dc.rr.com
Subject: EnCell report

Hey, Stan

Here is the info requested on Dan Andrews. -D.A -62 y/o male dx with acute phlebitis of right and left legs. Symptoms of chronic fatigue for 6 months prior, along with pain and swelling to feet, legs and ankles. D.A refused conventional medical treatment of hospitalization with heparin and bedrest. He was started on EnCell along with supporting nutritional therapy. Within a few days the swelling resolved and D.A expressed an increase in energy which continues to date. He had prior been drinking multiple cups of coffee and smoking 1-2 packs cigarettes to keep going with his long days. D.A. also refused to rest from his 12 hr days, on his feet days, even though this was also recommended.

Chris

Life Science Pharmacy

144 Route 17M, Ste #4, Harriman, New York 10926
(845) 781-7613 fax: (845) 781-7612

To All Concerned
May 9, 2008

Re: Methyl Pyruvate

My name is Scott Berliner and I am an integrative pharmacist with thirty years of experience in autoimmune issues, especially HIV. I am the clinical pharmacist at Friends in Deed in Manhattan, where I have introduced methyl pyruvate to study its efficacy. I have lectured on methyl pyruvate as I have on many nutritional topics that could benefit people with a variety of autoimmune issues and have been taking it myself for 30 months. I believe that this product can address one of the biggest issues I see in all of my patients, lack of energy.

As the consultant pharmacist to Beth Israel's Continuum Center and now Greenwich Hospital's Integrative Medicine Center, I am well connected in this field of medicine which is really where methyl pyruvate belongs. I look forward to introducing it as soon as the product is available. I will be the sole distributor of supplements to both of these facilities. Additionally, as the owner of Life Science, a compounding pharmacy, we are well equipped with technology to prepare necessary but unavailable formulas that will include methyl pyruvate

In addition to the study at Friends in Deed and my experience with about 50 patients taking the methyl pyruvate product, I myself have been using it at the recommended dose for 30 months with amazing increases in energy and stamina. My exercise has improved greatly due to the addition of this product to my daily regimen and I have seen that my patient's outcome has improved similarly. These patients with HIV/AIDS, Hepatitis C, MS, and Cirrhosis, as well have all noted the improvement in their health and energy. I have seen their viral loads come down, T-cell counts go up, liver panels improve to normal, and allergies go away - this all with an increase in energy from methyl pyruvate. I hope to be able to continue to supply this wonderful product to the many people that can benefit from it.

Lastly, I believe that in my quest for a better quality in my life, Encellon and their methyl pyruvate address many of these issues and the philosophy in which they were conceived is consistent with mine.

Scott Berliner R.Ph.
Integrative Pharmacist and Nutritional Educator

-----Original Message-----
From: maryloudriscoll@aol.com [mailto:maryloudriscoll@aol.com]
Sent: Sunday, May 11, 2008 12:31 PM
To: Bernadette
Subject: Re: FW: Encell

Mr. Antosh,

Participating in the Encell study has been very helpful to me; I was very surprised to learn that I had more energy after a few weeks and then months of taking Encell; I take it as Scott instructed: diluting 1cc of Encell in 10 ounces of water; then I mix an emergen-C packet, maybe even less than half a packet; it tastes delicious; it helps me to stay well hydrated; this is in addition to a healthy well balanced diet with adequate fruits, vegetables and proteins. usually I will drink around 32 ounces of water a day which would be 3.2 grams of Encell; sometimes, I will drink extra fluids in between though; I feel encell is an excellent formula.

Thank you for the opportunity to express my gratitude for allowing me to participate in this study,

Mary Louise

DONALD P. OROFINO, M.D.
100 Manetto Hill Road - Suite 309
Plainview, New York 11803
Tel. # (516) 433-3232 Fax # (516) 433-7802

October 25, 2006

Patient:

M.H. is a 65 year old patient with Primary Lateral Sclerosis, an upper motor neuron disease. She was first evaluated on July 29, 2005 when she was nearly unable to walk, stand or stop thigh muscle spasms, which were recurrent and incapacitating. In addition, her upper extremities were stiffening and progressively weakening.

Multiple evaluations at University medical centers were not able to stem the cause of deterioration. She pursued extensive alternative and allopathic evaluation and reconfiguration of hormonal and metabolic physiologic deficiencies without positive consequence. She was then placed on Methyl Pyruvate (Encell) at 2000md daily. The patient responded with remarkable increased strength of her upper extremities, increased standing and assisted walking occurred. Finally the muscle spasms diminished. This all occurred within two to three months and we continue to see modest alleviation of symptoms in the usual poor course of this disease.

M H gives her verbal approval of the accuracy of this document and her consent to disseminate this to EnCellon Inc .

This narrative was drafted by Dr. Donald Orofino after full disclosure and discussion by this patient.

Sincerely,

Donald P. Orofino, M.D.

Donald P. Orofino, M.D.
100 Manetto Hill Road - Suite 309
Plainview, New York 11803
Tel# (516) 433-3232 Fax # (516) 433-7802

October 30, 2006

RE: Mary DiPasquale

For many years Mary DiPasquale has had recurrent haltering voice, similar to Katherine Hepburn. For as many years she has had both an intention tremor and later in life a resting tremor. Her gait and balance at times were unsteady and therefore somewhat restrictive.

Symmetrel was helpful for a time with her motor function. The patient declined Sinemet, as she has an alternative approach regarding her healthcare, and declines pharmaceuticals. Despite all therapies, her Parkinsons symptoms increased.

Methyl Pyruvate (EnCell) was started at 2000mg daily on 11/15/05 and in three days her haltering voice became normal and she could script her name legibly for the first time in years. This is a true and unsolicited statement that Mary will attest to any time.

This narrative was drafted by Dr. Donald Orofino after full disclosure and discussion by this patient.

Sincerely,

Donald P. Orofino, M.D.

From: DandDJones57@aol.com [mailto:DandDJones57@aol.com]
Sent: Monday, May 05, 2008 4:51 PM
To: santosh@dc.rr.com
Subject: Encell Testimonials

My name is Donna and I am 57 yrs. old, my husband is Dave and he is 68 yrs. old. This is actually two testimonials for Encell.

In December '06, Dave was diagnosed by Mayo Clinic and UCLA Movement Disorder Clinic with MSA (Multiple Systems Atrophy) with Parkinson's type symptoms. We were told good-bye, good luck there is no cure, no hope. In February '07, Dave met with a Holistic Internist and started on a heavy vitamin therapy and detox regime. He was holding his own but not improving.

On February 27, '08, we met Stan Antosh and he introduced us to his Encell product. He explained how Dave's cells were most likely not making enough energy because of Dave's age and condition. He said that Encell would increase his cell's energy and their ability to function normally while repairing the damage

That day, Stan then gave Dave 1 ml of Encell with 16 ounces of water. We all saw an improvement within a half an hour in Dave's eyes, the volume of his voice and his face was not so rigid and had more expression.

Dave has been following Stan's protocol since then and Encell is its cornerstone. He takes 1ml three times a day. Dave is improving a little everyday and is very hopeful about the future and getting back to his golf game.

I am the second part of this testimonial. Two weeks into Dave's treatment, we met with Stan again. He suggested that I should start on the Encell because caregivers are easy targets for fatigue and depression. The next day I took Encell and immediately felt a tingle and rush of energy. I am now taking 1 ml of Encell twice a day along with Stan's vitamin therapy and I feel great. I have more energy to give to Dave and even have some left over for myself.

May 19, 2007

I am a pharmacist for 39 yrs, in business for myself from 1974-2002. I have been a compounding pharmacist for 21 yrs. I have been using EnCell since March 05. I have experience with Encell in about 200 patients. The consensus from the patients and their experience with EnCell while varied, is an increase in energy and stamina resulting in better all around health with relief from symptoms of their illness. Also, the increase in energy is noticed as an improvement in mood, mental clarity and the ability to concentrate. At my age I was amazed to notice a tremendous increase in my workouts and my aerobic conditioning in biking through the hills around my house. The people who have tried the Encell vary from a highly trained 34 year old man competing in water polo to a 94 year old man recovering from hip surgery.

Ronald E Partain, RPh, CCN

Methyl Pyruvate (EnCell) Testimonials

I have a heart condition (cardiomyopathy) and EnCell has benefitted me greatly. I have more endurance and less shortness of breath on exertion. My wife has noticed a big difference and thanks you also! This is an excellent product that should be considered for many chronic debilitating diseases.

Tom Klein, Pharm.D.

I am an 84-year-old widow who has been using your very effective EnCell for about a year now.

I must tell you that it as greatly improved my life and that of my mentally handicap son. Since I have added it to my son's and my supplemental program, we have noticed many benefits. When I recently moved to an Adult Community Country Club with a clubhouse that has a fully equipped gym, I noticed that my son and I could only do about 5 minutes on the Life Cycle machine. Once we Started using taking EnCell three times a day, we gradually noticed we both were able to increase our times on the cycle, now up to 20 minutes more!

One year ago, I underwent major surgery for an inflamed gall bladder that almost killed me. It took two months to recover and once I was at my new home, a friend recommended EnCell to my son and I.

We are most grateful for his recommendation since it has added to the quality of our lives daily. EnCell has been a blessing to both our lives.

Mrs. Esther P. Stame
Menifee, CA

Since using EnCell I have a lot more energy and a more positive mental attitude. My blood pressure, which was previously high, has now gone down and is a normal healthy level . On top of which I sleep so much better and wake up feeling totally refreshed.

Colin
Studio City, CA

Keeping up with my 4 year old daughter is a tough job that requires a lot of energy and patience. Throw in the full time 'corporate' job I started in November. This job requires a great deal of 'brain work' and requires me to be 'on' from the minute I arrive. The challenges of learning and maintaining a high level of job performance were draining the energy needed to give my daughter the quality of attention she and I both wanted.

Then came EnCell. No morning grogginess. In fact, I've quit coffee completely and don't feel the need for it, nor did I suffer any of the ill-effects that quitting caffeine can bring about. No mid-afternoon slump. I am able to fully concentrate, comprehend, and communicate effectively all day. My mood is upbeat all day long and into the evening.
I have the energy and attention to spend quality time with my daughter in the evenings — instead of a lump on the couch.

Julie H.
Palm Springs, CA

Since starting EnCell my blood pressure is now normal, unheard of in the past, my skin feels and looks healthy and I receive so many compliments about my eyes! I stopped using red-eye reduction products after a few weeks. Energy levels are higher but not hyper.

Mary
La Quinta, CA

My energy has gone from extremely low to extremely high. (I can now work 10-12 hours non stop). I used to wake up every 2-3 hours and now sleep soundly 6-7 hours. My Ph level used to run around 6, it is now 7or 7.5.
My blood pressure was 150/78 and is now runs consistently 112/ 65. Since I have ADD my focus can be scattered. I am better able to concentrate. The heat and humidity in the state of Virginia has usually wiped me out by the end of the day of business appointments.

Last year Virginia had the longest heat wave on record and I was not affected. My doctor has said that I looked great several times and he doesn't give compliments. I told him it was because of Encell and briefly explained what it has done for me. He wants to try some. I couldn't believe it!! Monday I will take him a week's worth.

EnCell is an amazing product and I feel most fortunate to have been able to acquire it. As an aging American facing the many health challenges we do, my hope would be for EnCell to be marketed quickly as to allow others to feel well in their declining years.

Brenda
Virginia

Thanks to the recommendation of a close friend, I have been using EnCell for almost a year and want to share my story. I am an 80-year-old diabetic who has had to deal with low energy at various times in my life. Since I have added EnCell to my supplements, I have noticed a couple of positive changes in my health.
Before I was not as physically active as I am now. Recently I have returned going to my local gym and am seeing an improvement in my low impact exercises. I last longer on the treadmill. My daily walks are longer and farther and must more enjoyable.

EnCell has been a blessing and I am most grateful for its existence. I would like to add my vote of confidence to your product and thank you for its creation.

Marie Ponce
Menifee, CA

My health had been on a steady declinesince my hysterectomy in 1992. I was so exhausted I would have to lie down between most activities and even unloading the dishwasher became a monumental chore. My exhaustion was so grave it affected not only business appointments but also phone calls and impacted every area of my life.
This tremendous decline in energy resulted even after consulting many physicians whose tests showed absolutely no problems.

By balancing my systems and adding Encell and vitamins to my diet I now feel unbelievably good. It is amazing that there are days when I can barely remember how ill I had been.

Brenda G. Fenn

I have been plagued with a water drinking problem, hard to get enough down. Encell is making my daily water intake easy. Additionally I am sleeping very soundly, have been a very light sleeper in the past, I won't go into my dreams, nothing more needs to be said.

Tim

Just wanted to let you know that Encell has been great. It's a fantastic intestinal cleanser for me. I wake up in the morning much earlier than usual and instead of boomeranging off the walls in a stupor I'm more alert and I feel a sense of well being which has been fairly non existent in the past few years. I do have a very active dream life that's blossomed out of the blue.

Marilyn

I have been using EnCell for the last couple of months. I am a single Mom of two children, which keeps me busy, and working full time. Since taking EnCell, I no longer feel rundown and I have more energy. I no longer drink coffee in the morning; EnCell has replaced the coffee without any cravings for the caffeine. I take Encell about 3 times a day. First when I wake up and then on my break at work, and then again before I leave work for the day.
It helps me maintain the daily work load that I carry alone.

Encell is a wonderful product, and I highly recommend it to others!

Gina F.

My energy level had always been very strong, my zest for life at times too full for words. I always viewed the world as the greatest place, and life fun.
About seven years ago I was diagnosed with M.S. It came as quite a shock to me, but I was determined not to let it get me down. I read all I could get my hands on and talked about it, then I began the usual or normal treatment routine. Taking the new drugs that we are "so fortunate" to have available to us.

But, as time went on I began to get very tired and living a very middle of the road existence. As always, I still saw the cup as half full. In reality, it wasn't. Daily activities were very difficult and I felt awful on the medicines I had been taking. I was put on an incredible nutrient regimen. I felt better and better and believe it or not the MRI I took showed actual improvements, which is supposedly unheard of. But, I still felt very tired and had a difficult time with fatigue and all the other symptoms that go along with M.S. But with the proper rest etc. I could manage it.

One day I was recommended to try EnCell. Not totally understanding what it was I tried it. I felt better than ever in a very short period of time, it was amazing to me the increase in energy and best of all I had no MS symptoms at all.

I felt so good I began to ride horses all the time. It was fantastic. Then one night I had a very serious accident. I suffered many broken bones, which required surgery and I had to sit and be still for weeks. During this time I was not taking EnCell. After 6 weeks off I started taking it again and suddenly in 3 - 4 days I did not have to take pain medicine anymore. I was able to improve beyond the Doctors wildest imaginations at my physical therapy - gaining motion and strength rapidly. Best of all my zest for life returned. I am ready to resume my life as a reading teacher and continue my research about children and learning styles.

I am very blessed to have had all of the experiences that I have endured and always to come out with such sunshine!
I hope to always have a supply of EnCell because it is such a miracle.

Lisa W.

Thank you for EnCell and the impact it seems to be having for my son in toxic metal excretion and microbial attack. As I indicated, Michael has taken all of the traditional metal chelators (DMSA, DMPS, EDTA, selenium) over the past 5 to 6 years. We have been tracking his urine and stool excretion levels of toxic metals, very closely with over 40 samples in the last 2 years. I recently ran 2 samples after having Michael on EnCell for 6 weeks. The toxic excretion levels were incredible; in some cases 10 to 20 times higher than we have ever seen with chelators. We kept all other variables in his protocol the same during this period, so we believe that EnCell is really a metals "dump". Michael also is being treated for lyme disease and I noticed that when he is on EnCell the immune attack seems to be much stronger just by observing the traditional die off symptoms (green stools, rash, fever, severe anxiety and mood swing.)

It has now become a cornerstone in Michael's protocol.

Robert Claeys

METALS	RESULT mg/kg	REFERENCE RANGE	PERCENTILE 68th 95th
Mercury	0.188	<.05 w/o amalgams*	
Mercury	0.188	<.5 with amalgams*	
Antimony	0.170	< 0.080	
Arsenic	3.31	< 0.30	
Beryllium	0.023	< 0.009	
Bismuth	664.3	< 0.050	
Cadmium	0.29	< 0.50	
Copper	36	< 50	
Lead	1.39	< 0.50	
Nickel	5.3	< 2.0	
Platinum	< dl	< 0.003	
Thallium	0.027	< 0.020	
Tungsten	0.071	< 0.090	
Uranium	0.253	< 0.120	

	RESULT % H_2O	EXPECTED RANGE	2SD LOW 1SD LOW MEAN 72.5% 1SD HIGH 2SD HIGH
% WATER CONTENT	86.2	60-85%	

Case Example: Diabetes

Preliminary Observation

Patient: 35 yr, male, diagnosed Type I Diabetes at 24 yr, 185 lbs, no exercise, poor diet, HbA1c: 8.5%-8.6%

Treatment: **EnCell** at 330mg, 2X/day for 3 months. No other changes.

Result: Increased waking energy. HbA1c: 7.3%.

Less than 1g of EnCell led to a >1% decrease in HbA1c

Methyl Pyruvate Diabetes Clinical Study

Donald P. Orofino MD, Tony Meduri PhD DSc, Ranya Alexander MD, PhD

METHYL PYRUVATE STUDY

Subjects: The parameters required for acceptance into the Methyl Pyruvate Diabetes Case Study are limited to individuals diagnosed with Type 1 or Type 2 Diabetes Mellitus. Additional specific major medical conditions may result in non-acceptance, to be determined by the medical team.

Title: The effects of ingested methyl pyruvate in decreasing HbA1c and insulin resistance of individuals with Type 1 or Type 2 Diabetes Mellitus.

Clinical Study Phase 1

Study duration: 90 days

Single center study:

The objective of this clinical trial is to quantify the effects (if any) of ingested methyl pyruvate (a dietary supplement) on intracellular energy levels required above baseline maintenance to lower HbA1c, insulin resistance and increase "noticeable energy" with improvement of symptoms in humans diagnosed to have Type 1 or Type 2 Diabetes Mellitus.

Number of subjects: 11

The tested product is methyl pyruvate liquid, 1cc/ml (1gram) dose diluted in 12 oz./water ingested orally 2 times per day for 90 days.

Reference therapy consists of one participant increasing their daily intake of water to equal the increased water intake of the control group when diluting their methyl pyruvate twice daily dose of 12 oz. water per dose.

This case study duration is for 90 days (from 5/07 – 8/07) with the option to continue and requires monthly visits with verbal feed-back as part of a comprehensive continuing care medical treatment program. This data, including all names, personal and medical information is to be held with the strictest of confidence. Used only for statistical compilation at the conclusion of this case study. Our goal is to determine the benefits of methyl pyruvate and bring relief for those with Type 1 or Type 2 Diabetes Mellitus.

There are no costs involved for the methyl pyruvate for participants, only an agreement to comply with the protocol schedule. All other medical care is part of the comprehensive continuing care medical treatment program and will be billed as usual.

Statistical method: Because of the low sample size (eleven total) we will enroll three participants to increase their water intake only as the placebo. Baseline HbA1c will be taken on day 0, day 30, day 60, day 90. Our reference is our review and knowledge of the participant's medical history and the subjective feedback and observations from the investigator, participants and spouse or family (if any) on the effects of methyl pyruvate on the various symptoms specific to each person.

1. This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedure.

1.1 **Background** Methyl pyruvate is a lipophilic derivative of pyruvate a natural product produced in the body. Methylation of pyruvate rendered is more available to cells and allows greater participation of an initiate of the tricarboxylic acid cycle (Krebs Cycle).

Anecdotal reports have shown that methyl pyruvate when taken orally, subjectively confers energy to the consumer presumably based on the increased adenosine triphosphate (ATP) production and enhanced efficiency of cellular oxidative phosphorylation. Pyruvate in effect "primes" the TCA pump. This process would, presumably, render mitochondria more productive in a shorter period of time and increase metabolism of glucose with subsequent insulin-responsive tissue GLUT4 transporter clearance of blood glucose, thereby lowering HbA1c and insulin resistance. Numerous studies have demonstrated the importance of normal GLUT4 expression and cellular localization in regulating glucose homeostasis. It is estimated that up to 70% of blood glucose is cleared by the GLUT4 insulin-responsive tissue muscle.

1.2 **Investigational Agent:** Methyl Pyruvate – The energy requirements of most cells supplied with glucose are fulfilled by glycolytic and oxidative metabolism, yielding ATP. A membrane-permeant analog, methyl pyruvate, in pancreatic beta cells, produced a block of KATP, a sustained rise in [Ca2+], and an increase in ATP driven insulin secretion 6-fold the magnitude of that induced by glucose.

1.3

Diabetes is a chronic disorder of glucose (sugar) metabolism caused by inadequate production or use of insulin, a hormone produced in specialized cells (beta cells in the islets of Langerhans) in the pancreas that allows the body to use and store glucose. It is a leading cause of death in the United States and is especially prevalent among African Americans.

Glycosylated Hemoglobin A1c, HbA1c is a test that measures the amount of glycosylated hemoglobin in your blood. Glycosylated hemoglobin is a molecule in red blood cells that attaches to glucose (blood sugar). You have more glycosylated hemoglobin if you have more glucose in your blood. The test is becoming the best measure of diabetic disease management and predictor of overall cardiovascular disease. Studies in the US and abroad have found that improved glycemic control benefits people with diabetes. In general, every percentage point drop in A1C blood test results (e.g., from 8.0% to 7.0%) reduces the risk of microvascular complications (eye, kidney, and nerve diseases) by 40%. (American Diabetes Association)

1.4 **Pre-Clinical data - Reports from 250 people between the ages of 18 – 92.**

The MP benefits reported:

> Immediate reservoir of energy and stamina
> Enhanced recovery between sets in a workout and between workouts
> Heightened sense of awareness, association and mental clarity
> Improved mood and ability to concentrate
> Ability to work longer and with fewer breaks
> Staying power
> Much greater endurance
> Overall higher performance and intensity outputs
> Rapid "bounce back" from stress... mental-physical

1.5 **Dose rational and risk and benefits.** Original dose (range of 2-6 grams per day) assessment was based on results of in-vitro insulin secretion studies. Quantitative comparisons of glucose, glutamine, glutamic acid, luceine, pyruvate and methyl pyruvate on pancreatic beta-cells established a base-line reference. This theory was subsequently validated by anecdotal reports. Possible negative side-effects may include, but are not limited to gastro esophageal reflux, esophageal irritation, Transient visual disturbance

2. **Study Objectives:** The objective of this observational trial is to quantify the effects (if any) of ingested methyl pyruvate (a dietary supplement) on intracellular ATP energy levels required above baseline maintenance. This process would, presumably, render mitochondria more productive in a shorter period of time and increase metabolism of glucose with subsequent GLUT4 transporter clearance of blood glucose, thereby lowering HbA1c and insulin resistance. The test is becoming the best measure of diabetic disease management and predictor of overall cardiovascular disease. Studies in the US and abroad have found that improved glycemic control benefits people with diabetes. In general, every percentage point drop in A1C blood test results (e.g., from 8.0% to 7.0%) reduces the risk of microvascular complications (eye, kidney, and nerve diseases) by 40%.

3. **Study design:** Monthly HbA1c testing at day 0, day 30, day 60, day 90.

3.1 Primary endpoints- to study the efficacy of methyl pyruvate on increasing intracellular energy levels required above baseline maintenance to lower HbA1c and insulin resistance with improvement of related symptoms in humans diagnosed to have Type 1 or Type 2 Diabetes Mellitus.

3.2 Secondary endpoint – to establish if the increase in energy is objectively "noticeable energy."

3.3 Tertiary endpoint- to underscore the taste and GI tolerability of the tested dosage of liquid methyl pyruvate.

4. Subject selectivity

4.1 Inclusion criteria: individuals diagnosed with Type 1 or Type 2 Diabetes Mellitus.

4.2 Exclusion criteria: Additional specific major medical conditions to be determined by the medical team such as cardiac, respiratory, metabolic disease or infections.

5. Methyl Pyruvate

5.1 Description: clear liquid with slight lactate odor and taste.

5.2 Dose and route of administration: 1cc/ml (1gram) dose ingested orally 2 times per day diluted in 12 oz. water for 90 days.

5.3 Packaging for dosing: 12 identical, labeled, commercial glass 120 ml. (4oz.) bottles containing 120 ml. of methyl pyruvate to be given to the participants on day 0, 60 day.

6. Participant's procedure: participants are instructed to measure with a 1 ml. eyedropper 1 cc/ml. (1gram) dose of Methyl Pyruvate and dilute in 12 oz. of water, mix and drink in the early am and mid afternoon. Participants are instructed to not alter or change any normal eating habits or sleeping, exercise, physical therapy, medication or medical care.

7. Safety and adverse effects: should participant become ill or infirmed, they are instructed to contact their primary care physician. All adverse events must be recorded.

7.1 Stopping rules: Participants will be informed that they may stop at any time, but record the date.

Summary:

Methyl Pyruvate Diabetes Clinical Study Validates Efficacy of Methyl Pyruvate in decreasing HbA1c and insulin resistance of individuals with Type 1 or Type 2 Diabetes Mellitus.

Trial Design: Single center clinical study with 11 humans diagnosed with Type 1 or Type 2 Diabetes Mellitus.

Primary Endpoints: Study the efficacy of ingested methyl pyruvate in decreasing HbA1c of individuals with Type 1 or Type 2 Diabetes Mellitus.

Trial Results: Confirmed in clinical setting a decrease of HbA1c and insulin resistance:

11 Patients: Type I & II Diabetes (HbA1c between 5.7 – 12.1)

Treatment with methyl pyruvate at 2 g, 2X/day for 3 months. No other changes.

Result: No SAEs or AEs. No relevant changes in: Total protein, Albumin, Globulin, A/G ratio, BUN, Calcium, Iron, Chloride, Calcium, Bilirubin, Alk Phos, AST, Phosphorus, G-GTP, Cholesterol, WBC, RBC, Creatinine, BP, or weight.
However:

Average starting HbA1c: 7.5
Average 1 month HbA1c: 7.0
Average 2 month HbA1c: 7.1
Average 3 month HbA1c: 6.5

Three months of methyl pyruvate has lead to a decreased risk of:
CV disease by >20%
Micro-vascular disease by >40%
Death by >25%

Conclusion from Study: Methyl Pyruvate lowers HbA1c, insulin resistance and blood glucose in individuals with Type 1 or Type 2 Diabetes Mellitus and engenders an increase in "noticeable energy" promoting a feeling of well being with improvement of related symptoms of Diabetes Mellitus.

Subject: Diabetic Study on Donald Orofino's Patients

Diabetic Study on Donald Orofino's Patients

Name	Date	HBA1c	Weight	B/P	+/-
Broderick, John	5/4/07	9.9	234	118/80	N/A
Di Adele	5/4/07	6.7	236	144/88	
	6/1/07	7.0	235	160/84	+.3
Di Vito	5/4/07	7.8	216	124/80	
	6/1/07	8.5	216	128/70	+.7
J Sarah	5/4/07	9.9	232	168/100	
	6/1/07	11.2	233	199/106	+1.3
(repeat 10 min.)				140/82	
K Barbara	6/1/07	9.1	188	118/78	N/A
M Henry	5/4/07	7.0	257.5	152/78	
	6/1/07	7.1	259	170/80	+.1
P Johanna	5/4/07	6.4	160	140/80	N/A
P Nick	5/4/07	12.1	286	150/72	
	6/1/07	11.1	290	150/70	-1
R Joetta	5/4/07	5.7	158.5	180/80	
	6/1/07	6.1	158	132/66	+.4
S Moses	5/4/07	6.5	220	130/70	
	6/5/07	5.3	223	150/82	-1.2
(repeat)				140/80	
W Donald	5/4/07	5.7	160	120/68	
	6/1/07	5.7	151	124/82	---
C , Winston	6/29/07	7.6			

Participants Call Sheet

(alphabetically)

DATE:

	5/4/07	6/1/07	6/29/07	7/31/07	
Broderick, John 516- 921- 6235 A1C	7.9	6.5 Lab 7.0 HS	6/11/07 ~~6.5~~ 7.9	7/12/07 6.4	7/31/07 6.3
Di Adele • 516- - 0440 2/21/07 6.6	6.7	7.0	7.7	6.3	
Di Vito • 516- - 0440	7.8	8.5	8.3	7/31/08 7.6	
J Sarah • 516- 0900	9.9	11.2	~~8.~~	7/26/07 9.9	
K. Barbara Juvenile 516- 6137	—	9.1	6.5	7/26/08 7.5	
M Henry 516- 6952	7.0	7.1	6.4	7/25/07 5.8	
P Johanna • 516- 2021	6.4	6.2	7/16/07 7.4		
P Nick 516- - 0025	12.1	11.1	9.9	7/26/07 10.2	
R Joetta 631- - 5092	5.7	6.1	6.0	7/17/08 5.5	
S Moses 516- - 9899	6.5	5.3	6.4	5.6	
W Donald 516- 3668	5.7	5.7	~~5.5~~	7/17/07 5.1	
W Connor	—	—	7.6	7/24/07 7.0	

• Poor Compliance •

Participants Call Sheet

(alphabetically)

DATE:

	5/4/07	6/1/07	6/29/07	7/31/07	
Broderick, John 516- - 6235 A1C	7.9	6.5 LAB 7.0 US	6/11/07 ~~6.8~~ 7.9	7/12/07 6.4	7/31/07 6.3
Di Adele 516- - 0440					
Di Vito 516- - 0440					
J Sarah 516- - 0900					
K Barbara Juvenile 516- - 6137	—	9.1	6.5	7/26/08 7.5	
M Henry 516- - 6952	7.0	7.1	6.4	7/25/07 5.8	
P Johanna 516- - 2021					
P Nick 516- 0025	12.1	11.1	9.9	7/26/07 10.2	
R Joetta 631- - 5092	5.7	6.1	6.0	7/17/08 5.5	
S Moses 516- - 9899	6.5	5.3	6.4	5.6	
W Donald 516- -3668	5.7	5.7	~~5.5~~	7/17/07 5.1	
W Conner	—	—	7.6	7/24/07 7.0	

DONALD P. OROFINO, M.D.
100 MANETTO HILL ROAD – SUITE 309, PLAINVIEW, NEW YORK 11803
TEL# (516) 433-3232

Glycosylated Hemoglobin (HbA1c) Study
Confidential Patient Information

Name: [illegible] Sex: M or F Age: 70

Email: _____ Phone: 921-6235

Have you been diagnosed with any of the following conditions?

Type I, Insulin-Dependent Diabetes Yes_____ No_____
Type II, Adult Onset Diabetes Yes X No_____
Syndrome X/Metabolic Syndrome Yes_____ No_____
Other conditions_____

Please give approximate date(s) of diagnoses. APRIL - 2002

Are you taking any medications? Yes X No_____

Please list the names of all medications you are currently taking.

Please list the names of all vitamins, minerals, essential fatty acids, herbs, or other supplements you are currently taking.

Do you test your blood sugar? Yes_____ No ✓
If yes, how often, and what were your most recent results?

_____

Will you be willing to continue testing your blood sugar during the study and share your results with us? Yes_____ No ✓

Have you ever had your HbA1c tested? Yes_____ No_____ DON'T KNOW
If yes, please indicate your last known test result and when it was measured.

_____

7.31.07				
6.3	HbA1c at first visit: 7.9	2nd (28 days): 6.5 lab 7.0 VA	3rd (56 days): 7.9	6.4
225 LBS	Weight at first visit: 234	2nd (28 days): 229	3rd (56 days): 229	224
118/78	Blood pressure at first visit: 118/80 (RT) seat	2nd (28 days): 110/80 6/11/07 ✓	3rd (56 days): 110/72	140/84
	Date 5/4/07	6/11/07 10:00	6/29/07	7/17/07 BMP

7/31/07: Pt finally using Encell 2x/d → ↓↓ HgbA1c
w/ real Δ c diet no exercise
SP O.D. companches TODAY.

DONALD P. OROFINO, M.D.
100 MANETTO HILL ROAD – SUITE 309, PLAINVIEW, NEW YORK 11803
TEL# (516) 433-3232

Glycosylated Hemoglobin (HbA1c) Study
Confidential Patient Information

Name: GILBRIDE Sex: M or F Age: 70

Email: _____ Phone: 516 921-6235

Have you been diagnosed with any of the following conditions?

Type I, Insulin-Dependent Diabetes Yes_____ No_____
Type II, Adult Onset Diabetes Yes X No_____
Syndrome X/Metabolic Syndrome Yes_____ No_____
Other conditions_____

Please give approximate date(s) of diagnoses. APRIL - 2002

Are you taking any medications? Yes X No_____

Please list the names of all medications you are currently taking.

Please list the names of all vitamins, minerals, essential fatty acids, herbs, or other supplements you are currently taking.

Do you test your blood sugar? Yes_____ No ✓
If yes, how often, and what were your most recent results?

_____

Will you be willing to continue testing your blood sugar during the study and share your results with us? Yes_____ No ✓

Have you ever had your HbA1c tested? Yes_____ No_____ DON'T KNOW
If yes, please indicate your last known test result and when it was measured.

_____

HbA1c at first visit: 7.9	2nd (28 days): 7.0	3rd (56 days):_____
Weight at first visit: 234	2nd (28 days): 229	3rd (56 days):_____
Blood pressure at first visit: 118/80 (R) Seat	2nd (28 days): 110/80 ✓	3rd (56 days):_____

Date 5/4/07 6/11/07 10:00 @ 6/29/07

DONALD P. OROFINO, M.D.
100 MANETTO HILL ROAD – SUITE 309, PLAINVIEW, NEW YORK 11803
TEL# (516) 433-3232

Glycosylated Hemoglobin Study
Consent Form for Taking Methyl Pyruvate (MP)

I, [illegible], agree to participating in this 2 month study on the use of EnCell to evaluate changes in my weight, blood pressure, and HbA1c.

I have received information on the potential health benefits of EnCell, and feel satisfied that I've had all my questions answered. ✓

I agree to take the EnCell, as prescribed, for a period of 2 months. ✓

I agree to take the water, as prescribed, for a period of 2 months. ✓

I agree to having my weight, blood pressure, and HbA1c recorded at the beginning of the study, at one month into the study, and at the end the study at two months. ✓

I agree to notify the investigators of this study by phone, or by email at EnCell@aol.com, if I decide to drop out of the study. ✓

I agree to filling out the survey at the beginning of the study, at one month, and at two months. ✓

I agree to notify the investigators of this study by phone, or by email at EnCell@aol.com, if I have any sudden changes in my health. ✓

I agree to not modify my diet, supplements, and exercise programs over the next two months. ✓

I understand that EnCell is a dietary supplement and has not been approved by the FDA for consumption. ✓

I understand all my information will be kept confidential: ✓

Name: [signature] Date: 8/4/07

Signature: [illegible]

BioReference LABORATORIES

DONALD OROFINO MD
100 MANETTO HILL RD#309
PLAINVIEW, NY 11803
(516)433-3232 (S3910)

T O R

-PRELIMINARY-

DOB 04/06/1937

NAME	PATIENT I.D./ROOM NO.	PHONE	DOCTOR / GROUP NAME
BRODERICK, JOHN J	094283960	( )921-6235	OROFINO, DONALD

LAB I.D. NO.	DATE COLLECTED	DATE RECEIVED	DATE OF REPORT	AGE	SEX
105222142	07/31/2007	07/31/2007 03:31	08/02/2007 07:05	70 Y	M

Test Description	Result	Abnormal	Reference	Units
CHEMISTRY				
Glucose		**153 HI**	70-109	mg/dL
Sodium	143		133-145	mmol/L
Potassium	3.9		3.3-5.3	mmol/L
Chloride	104		96-108	mmol/L
CO2	23		21-29	mmol/L
BUN		**26 HI**	7-25	mg/dl
Creatinine		**1.5 HI**	0.6-1.3	mg/dl
BUN/Creat Ratio	17.3		10-28	
Calcium	9.3		8.4-10.4	mg/dl
ALT (SGPT)	19		< 40	u/L
CARDIOVASCULAR/LIPIDS				
hs C-RP	1.7		SEE BELOW	

****

HIGH SENSITIVITY CRP (hsCRP) (test#3320) REFERENCE RANGES

RANGE (mg/L)	Relative Risk of Future MI or Stroke
<1.0	LOW
1.0-3.0	AVERAGE
>3.0	HIGH

NOTE: An elevated hsCRP result along with an elevated total cholesterol (TC) result provides greater predictive value for relative risk of stroke, MI or peripheral vascular disease than either risk factor alone. (For patients below the 75th percentile with elevated TC AND hsCRP a five fold increase in relative risk was noted vs TC or hsCRP alone [2.3 fold and 1.5 fold respectively]). hsCRP results of >10 mg/L suggest current infection/inflammation. Patients in this range should be retested 2-3 weeks following resolution of the infection.

****

MISCELLANEOUS			
CRP	<0.3		<0.5 mg/dL
HGB. A1c(glycohgb)	6.4		< 6.0%

****

HEMOGLOBIN A1c RANGES(%)	GLUCOSE CONTROL INDEX
< 6.0%	Non-Diabetic Level
< 7.0%	Diabetic Control

Printed: 08/02/2007 07:58

Continued on Next Page

James Weisberger, MD
LABORATORY DIRECTOR

481 Edward H. Ross Drive
Elmwood Park, NJ 07407
(800) 229-LABS

Methyl Pyruvate Parkinson's Observational Study

Ron Partain RPH, C.C.N., Ranya Alexander MD PhD, James Perkins DC QME
Tony Meduri PhD DSc, Kevin Dunn DC QME

METHYL PYRUVATE STUDY

Subjects: The parameters required for acceptance into the methyl pyruvate Parkinson's Case Study are limited to individuals diagnosed with Parkinson's or affected with Parkinson's symptoms. Additional specific major medical conditions may result in non-acceptance, to be determined by the medical team.

Title: The effects of ingested methyl pyruvate on individuals with Parkinson's or Parkinson's symptoms.

Observational Study Phase 1

Study duration: 180 days

Single center study:

The objective of this observational trial is to quantify the effects (if any) of ingested methyl pyruvate (a dietary supplement) on intracellular energy levels required above baseline maintenance to produce ATP driven dopamine and "noticeable energy" with improvement of symptoms in humans diagnosed to have Parkinson's Disease or Parkinson's symptoms.

Number of subjects: 15

The tested product is methyl pyruvate liquid, 1cc/ml (1gram) dose diluted in 12 oz./water ingested orally 2 times per day for 180 days.

Reference therapy: none.

This case study duration is for 180 days (from 3/05 – 9/05) and requires bi-monthly written/verbal feed-back form completion. This data, including all names, personal and medical information is to be held with the strictest of confidence. Used only for statistical compilation at the conclusion of this case study. Our goal is to determine the benefits of methyl pyruvate and bring relief for those with Parkinson's.

There are no costs involved for participants other than time and an agreement to comply with the protocol schedule.

Statistical method: Because of the low sample size (fifteen total) and our commencement of the study we do not have access to the PDQ 39. PDQ 39 is the most widely used standardized, validated questionnaire to measure improvement or worsening of symptoms in patients diagnosed with Parkinson's disease. Our reference is our review and knowledge of PDQ 39 and the subjective feedback and observations from the investigators, participants and spouse or family (if any) on the effects of methyl pyruvate on the various symptoms specific to each person.

1. This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedure.

1.1 **Background** Methyl pyruvate is a lipophilic derivative of pyruvate a natural product produced in the body. Methylation of pyruvate rendered is more available to cells and allows greater participation of an initiate of the tricarboxylic acid cycle (Krebs Cycle).

Anecdotal reports have shown that methyl pyruvate when taken orally, subjectively confers energy to the consumer presumably based on the increased adenosine triphosphate (ATP) production and enhanced efficiency of cellular oxidative phosphorylation. Pyruvate in effect "primes" the TCA pump. This process would, presumably, render mitochondria more productive in a shorter period of time and increase production of dopamine, which requires ATP, via a non-artificial nutritional mechanism, which does not involve pharmaceutical drugs and their negative side-effects.

1.2 **Investigational Agent:** Methyl Pyruvate – The energy requirements of most cells supplied with glucose are fulfilled by glycolytic and oxidative metabolism, yielding ATP. A membrane-permeant analog, methyl pyruvate, in pancreatic beta cells, produced a block of KATP, a sustained rise in [Ca2+], and an increase in ATP driven insulin secretion 6-fold the magnitude of that induced by glucose.

Parkinson's disease occurs when a group of cells in an area of the brain called the substantia nigra begin to malfunction and die. These cells in the substantia nigra produce a chemical called dopamine. Dopamine is a neurotransmitter, or chemical messenger, that sends information to the parts of the brain that control movement and coordination. When a person has Parkinson's disease, their dopamine-producing cells begin to die and the amount of dopamine produced in the brain decreases. Messages from the brain telling the body how and when to move are therefore delivered more slowly, leaving a person incapable of initiating and controlling movements in a normal way.

Parkinson's disease can also cause several different symptoms. The specific group of symptoms that an individual experiences varies from person to person. Some of the most common symptoms of Parkinson's disease are:

- tremor of the hands, arms, legs, jaw and face
- rigidity or stiffness of the limbs and trunk
- bradykinesia or slowness of movement
- postural instability or impaired balance and coordination

ATP and Dopamine

There is abundant evidence that ATP -sensitive K+ (KATP) channels link metabolic state to ATP, protein synthesis and dopamine cell excitability. The regulation of KATP channels in substantia nigra dopamine neurons by hydrogen peroxide (H2O2), which is produced in all cells during aerobic metabolism is omnipresent. Blockade of KATP channels or depletion of intracellular H2O2 increases the spontaneous firing rate of all dopamine neurons tested. Thus, endogenous H2O2 modulates neuronal activity via KATP channel opening, thereby enhancing the reciprocal relationship between metabolism and excitability.

Dopamine and Parkinson's disease: Dopamine is a chemical naturally produced in the body. In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary .Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, since dopamine cannot cross the blood-brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and Dopa-Responsive Dystonia, a synthetic precursor to dopamine such as L-DOPA can be given, since this will cross the blood-brain barrier.

Functions of dopamine in the brain

Role in movement

Dopamine is critical to the way the brain controls our movements and is a crucial part of the basal ganglia motor loop. Shortage of dopamine, particularly the death of dopamine neurons in the nigrostriatal pathway, causes Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

Role in cognition and frontal cortex function

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder and negative schizophrenia.

Role in regulating prolactin secretion

Dopamine is the primary neuroendocrine regulator of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion.

1.3 **Pre-Clinical data - Reports from 25 people between the ages of 29 - 76**

The MP benefits reported:

> Immediate reservoir of energy and stamina
> Enhanced recovery between sets in a workout and between workouts
> Heightened sense of awareness, association and mental clarity
> Improved mood and ability to concentrate
> Ability to work longer and with fewer breaks
> Staying power
> Much greater endurance
> Overall higher performance and intensity outputs
> Rapid "bounce back" from stress... mental-physical

1.4 **Dose rational and risk and benefits.** Original dose (range of 2-6 grams per day) assessment was based on results of in-vitro insulin secretion studies. Quantitative comparisons of glucose, glutamine, glutamic acid, luceine, pyruvate and methyl pyruvate on pancreatic beta-cells established a base-line reference. This theory was subsequently validated by anecdotal reports. Possible negative side-effects may include, but are not limited to gastro esophageal reflux, esophageal irritation, Transient visual disturbance

2. **Study Objectives:** The objective of this observational trial is to quantify the effects (if any) of ingested methyl pyruvate (a dietary supplement) on intracellular energy levels required above baseline maintenance to produce ATP driven dopamine and "noticeable energy" with improvement of symptoms in humans with Parkinson's Disease or Parkinson's symptoms.

3. **Study design:** observation with reference of PDQ 39.

3.1 Primary endpoint - to study the efficacy of methyl pyruvate objectively with reduction in symptoms in humans with Parkinson's Disease or Parkinson's symptoms.

3.2 Secondary endpoint - to study the efficacy of methyl pyruvate objectively as an increase in "noticeable energy".

3.3 Tertiary endpoint - to underscore the taste and GI tolerability of the test dosage of liquid methyl pyruvate.

4. **Subject selectivity**

4.1 Inclusion criteria: individuals diagnosed with Parkinson's or affected with Parkinson's symptoms.

4.2 Exclusion criteria: Additional specific major medical conditions to be determined by the medical team such as cardiac, respiratory, metabolic disease or infections.

5. **Methyl Pyruvate**

5.1 Description: clear liquid with slight lactate odor and taste.

5.2 Dose and route of administration: 1cc/ml (1gram) dose taken orally 2 times per day diluted in 12 oz. water for 180 days.

5.3 Packaging for dosing: 15 identical, labeled, commercial glass 120 ml. (4oz.) bottles containing 120 ml. of methyl pyruvate to be given to the participants on day 0, day, 60, day 120, .

6. **Participant's procedure:** participants are instructed to measure with a 1 ml. eyedropper 1cc/ml. dose of Methyl Pyruvate and dilute in 12 oz. of water and ingest in the early morning, and mid-afternoon. Participants are instructed to not alter or change any normal eating habits or sleeping, exercise, physical therapy, medication or medical care.

7. Safety and adverse effects: should participant become ill or infirmed, they are instructed to contact their primary care physician. All adverse events must be recorded.

7.1 Stopping rules: Participants will be informed that they may stop at any time, but record the date.

Summary:

Methyl Pyruvate Parkinson's Case Study Validates Efficacy of Methyl Pyruvate in improving or eliminating symptoms of Parkinson's disease.

Trial Design: Observational study with 15 humans diagnosed with Parkinson's disease or suffering from Parkinson's symptoms over 180 days.

Primary Endpoints: Study the Efficacy of Methyl Pyruvate in improving symptoms of Parkinson's disease.

Trial Results: Reported/observed improvement or elimination of symptoms.

1. tremor of the hands, arms, legs, jaw and face
2. rigidity or stiffness of the face, limbs and trunk
3. slowness of movement, talking.
4. impaired balance and coordination

Conclusion from Study: Methyl Pyruvate engenders both an increase in "noticeable energy" promoting a feeling of well being and improvement or elimination of symptoms in humans with Parkinson's disease or Parkinson's symptoms